should apply to postpartum bleeding and clinical situations such as trauma and postoperative bleeding. This area requires further study.

As with the effects of haematocrit/haemoglobin on primary haemostasis, data on the contribution of haematocrit to viscoelastic clot quality are not PPH specific. Studies in this area may be interesting, although not clinically useful for coagulation management. In clinical practice, the aim should be to optimize erythrocyte levels based on the measurement of haemoglobin/haematocrit, and clot formation based on appropriate coagulation test results; with all treatment decisions made in the context of the specific clinical situation and the individual patient’s condition.

**Declaration of interest**

The authors have the following conflicts of interest to declare: C.S. is an employee of CSL Behring and has received travel support from Haemoscope Ltd (former manufacturer of TEG), and speaker honoraria and/or research support from Tem International and CSL Behring. R.E.C. has received speaker honoraria from CSL Behring and Novo Nordisk and research support from Tem International. P.W.C. has received speaker honoraria from CSL Behring and Novo Nordisk and research support from Tem International.

C. Solomon1*
R. E. Collis2
P. W. Collins2
1Salzburg, Austria
2Cardiff, UK
*E-mail: cristina.solomon@cslehring.com

3 Crowley JP, Metzger JB, Valeri CR. The volume of blood shed during the bleeding time correlates with the peripheral venous hematocrit. *Am J Clin Pathol* 1997; 108: 579–84

doi:10.1093/bja/aet137

**Observational studies are not reliable enough when making decisions about individual patient care**

Editor—We read with concern Koster and colleagues’1 observational study of tranexamic acid and its association with increased rate of seizures and in-hospital mortality after heart surgery. Unfortunately, it is reminiscent of the beginnings of the sorry tale of aprotinin that led to its licence being suspended by drug regulatory agencies around the world.2 Similar observational studies led to concerns about the safety of aprotinin despite there being overwhelming evidence of its efficacy to reduce blood loss and transfusion and no evidence of increased incidences of adverse events from a meta-analysis of randomized controlled trials (RCTs).3 The final nail in the coffin to lead to the suspension of the licence for aprotinin was the BART study, which was an RCT, which found aprotinin to be associated with a higher mortality than the lysine analogues including tranexamic acid.4 However, a subsequent review of the evidence by Health Canada and other health regulatory agencies around the world discredited the evidence from the observational studies.2 In addition, when the BART trial was reviewed and re-analysed by Health Canada, there was no difference in mortality between aprotinin and the lysine analogues. Consequently, Health Canada lifted the suspension of aprotinin’s licence in 2012 and the European Medicines Agency has also recommended to the EU that the suspension of the licence for aprotinin should be lifted.2

Great caution must be taken when interpreting the findings from any study that uses an observational design, such as Koster and colleagues have used, as it has great inherent bias that cannot be overcome by statistical adjustment. Also, observational studies should not be used as the basis for changing accepted clinical practice. When making decisions about using or losing a drug such as tranexamic acid, we should rely on the large body of robust evidence of efficacy and safety that precedes the observational
study by Koster and colleagues. This evidence comes from a very large number of RCTs and their meta-analysis and demonstrates that tranexamic acid safely reduces blood loss and transfusion associated with cardiac surgery.

Declaration of interest
None declared.

R. P. Alston*  
V. McMullan  
Edinburgh, UK  
*E-mail: peter.alston@ed.ac.uk


doi:10.1093/bja/aet138

Safety of antifibrinolytic therapy during cardiac surgery and randomized controlled trials

Reply from the authors
Editor—We have read the thoughts of Drs Alston and McMullan regarding our article1 with great interest and agree with their reflections concerning the limitations of the results of observational studies. We have outlined this in a response2 to a previous letter and will avoid repetition in this regard.

However, the aprotinin tragedy, on which the final curtain has not fallen yet, demonstrates the limitations of the current concept of investigator-initiated or industry-sponsored randomized controlled trials (RCTs) to elucidate the safety profile of drugs in the multifaceted setting of complex cardiac surgery. The Blood Conservation Using Anti-fibrinolytics in a Randomized Controlled Trial (BART) was well published, but unfortunately not well performed. After review of all data and viewing imbalances in the grouping, Health Canada3 and the European Medicines Agency (EMA)4 lifted the suspension of aprotinin from the market, and have authorized the use of aprotinin only for basic coronary artery bypass grafting (CABG) surgery. Apparently, we all agree that effective blood conservation strategies are especially needed in the setting of complex cardiac surgery. Unfortunately, taking into account all available current data, both agencies expressed their concerns regarding aprotinin safety in complex cardiac surgery. Further studies into this matter are required. So, what does this mean in the end? The answer is evident: although aprotinin has been studied over decades in dozens of RCTs, and despite multiple sophisticated systematic reviews and meta-analyses, only drug effectiveness could be clearly demonstrated. These studies obviously failed to establish a clear safety profile, particularly in complex procedures. Complex cardiac surgery is performed using various different surgical and perfusion strategies. Additionally, patients most likely have numerous co-morbidities. Therefore, in this extremely heterogeneous setting, very high patient numbers are needed to clearly establish drug safety including effects on special organ systems.

A possible solution has been suggested by the EMA—the establishment of an international European register. Structured reporting of sophisticated sets of data from national key study centres may help to create such a large database. If these data produce suspicion of adverse drug effects, the pharmaceutical industry may be forced to initiate adequately powered RCTs to maintain authorization of the product in the special setting. Alternatively, industry and national insurance and health agencies may be asked to invest resources in a fund, which then is powered to perform adequate studies. The advantage of such a strategy would be that drug safety monitoring is more independent from the commercial interests of the pharmaceutical industry. This might guarantee that even older, well-established, and relatively inexpensive drugs such as tranexamic acid are continuously monitored.

The limitations of size and performance of the RCTs outlined for aprotinin also apply for tranexamic acid. Data, such as ours, show that, to date, the safety profile of tranexamic acid in the setting of complex surgery is inadequately studied. Therefore, we believe that an international register, not only for aprotinin, but also for the use of tranexamic acid in complex cardiac surgery, is badly needed. This seems to be all the more important as new alternative agents are not on the horizon. The development of possible successor drugs in cardiac surgery, such as the kalikrein inhibitor ecallantide and the antifibrinolytic agent MDCO-2010, has recently been stopped because of safety concerns.

Declaration of interest
None declared.

A. Koster*  
A. Zittermann  
U. Schirmer  
Westphalia, Germany  
*E-mail: akoster@hdz-nrw.de